

MULTIPLE AGENT DIABETES THERAPYField of the Invention

5 The present invention relates to pharmaceutical compositions useful in the treatment of diabetes, and more particularly to compositions useful in treating both diabetes and one or more side effects thereof. The present invention also relates to methods of treating diabetes using such compositions.

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Background of the Invention

Diabetes mellitus is a metabolic disorder characterized by chronically elevated levels of blood glucose, or hyperglycemia, which results from a reduction or absence of activity of the peptide hormone insulin. Insulin, which is produced and secreted by the beta cells of the pancreas, promotes the utilization of glucose and is essential to the maintenance of blood levels of glucose within the normal physiological range.

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Included within the scope of the term diabetes mellitus are two states: Type 1, also known as insulin-dependent diabetes mellitus (IDDM), and Type 2, or non-insulin-dependent diabetes mellitus (NIDDM). Type 1 diabetes is characterized by a deficiency or absence of insulin, such that the level of blood glucose cannot be maintained within the normal range, and must be treated by administration of insulin to the patient. Type 2 diabetes is characterized by either or both a state of insulin resistance or impaired insulin sensitivity or reduced insulin secretion, that is, a state in which insulin does not produce the expected decrease in blood glucose concentrations, resulting in hyperglycemia.

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Insulin and insulin analogs are commonly administered to diabetic patients, particularly Type 1 patients, in an injectable composition which comprises a pharmaceutically acceptable carrier and typically one or more conventional excipients. It is believed to be desirable to include in such compositions one or more peptides, in particular peptides that are naturally secreted by the pancreas

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together with insulin in non-iabetics. Such peptides are herein referred to as "insulin-related peptides".

5 One problem that is expected to arise in preparing such compositions is that most peptides are not as stable thermally as insulin. A need therefore exists for a thermally stable composition that includes insulin or an insulin analog together with at least one insulin-related peptide, peptide fragment or peptide analog.

10 Certain therapies for Type 2 diabetes do not require the administration of insulin. Such therapies, however, typically act by stimulating the release of insulin from the pancreatic beta cells. In these therapies, the pancreas can be subjected to undesirable stress. A need therefore also exists for an improved composition that does not cause excessive stress to the pancreas of the patient
15 to whom the composition is administered.

A need also exists for method of preparing such compositions and administering such compositions to a patient.

Summary of the Preferred Embodiments

20 In accordance with one aspect of the present invention, there is provided a pharmaceutical composition that includes at least two of agents chosen from the group of agents i) - iii). In the inventive composition, agent i) is selected from the group consisting of an insulin, an insulin analog or a physiologically active
25 fragment of the insulin or insulin analog, agent ii) is selected from the group consisting of an insulin-related peptide, an insulin-related peptide analog, a physiologically active insulin-related peptide fragment, or a physiologically active insulin-related peptide analog fragment, and agent iii) is an insulin sensitizer.

30 According to one more particular embodiment, the inventive composition includes agents i) and ii) above. More particularly, the composition further includes a pharmaceutically acceptable non-ionic surfactant.

35 According to another more particular embodiment, the inventive composition includes agents i) and iii) above.

According to another more particular embodiment, the inventive composition includes agents ii) and iii) above. This embodiment is beneficially employed in treating Type 2 diabetes.

5 In accordance with another aspect of the present invention, there is provided a pharmaceutical composition that includes at least one agent selected from the group consisting of an insulin, an insulin analog, a physiologically active insulin fragment and a physiologically active insulin analog fragment, and at least one agent selected from the group consisting
10 of an insulin-related peptide, an insulin-related peptide analog, a physiologically active insulin-related peptide fragment and a physiologically active insulated-related peptide analog fragment. The second agent has a hydrophobic portion that is coated with a pharmaceutically acceptable non-ionic surfactant.

15 In accordance with a further aspect of the present invention, methods of treating diabetes are provided that include the step of administering to a patient in need of such treatment the foregoing pharmaceutical compositions.

According to more specific embodiments, the compositions are
20 administered to the patient by a medication infusion pump. Preferably, the compositions are continually administered to the patient.

In accordance with still another aspect of the present invention, a method of treating diabetes is provided that includes the step of administering to a patient in need of such treatment at least two
25 pharmaceutical compositions chosen from the group of compositions a)-c). Composition a) includes at least one insulin, insulin analog or fragment thereof as described herein. Composition b) includes at least one insulin-related peptide, peptide analog or fragment thereof. Composition c) includes at least one insulin sensitizer. Each composition also includes a
30 pharmaceutically acceptable carrier.

In more specific embodiments, each composition is administered using a separate delivery device, in particular an external or internal medication infusion pump, and at different rates. Preferably each composition is administered continually.

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In one particular preferred embodiment, compositions a) and b) are administered to the patient. In this embodiment, composition b) preferably further includes at least one pharmaceutically acceptable non-ionic
5 surfactant.

Methods of making the inventive compositions are also provided.

Other objects, features and advantages of the present invention will become apparent to those skilled in the art from the following detailed description. It is to be understood, however, that the detailed description
10 and specific examples, while indicating preferred embodiments of the present invention, are given by way of illustration and not limitation. Many changes and modifications within the scope of the present invention may be made without departing from the spirit thereof, and the invention includes all such modifications.

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Detailed Description of the Preferred Embodiments

It has been discovered that the administration of two or more distinct types of agent, in multiple agent pharmaceutical compositions as described herein or in separate compositions that are coadministered or sequentially
20 administered, e.g, via medication infusion pumps, is effective in treating both diabetes and one or more diabetes side-effects.

As used herein, an "insulin analog" is a peptide that has insulin-like physiological activity, i.e., binds an insulin receptor and lowers blood glucose, and that includes one or more amino acids different from the amino
25 acid sequence of a naturally occurring insulin. Likewise, an "insulin-related peptide analog" is a peptide that has the physiological activity of an insulin-related peptide and an amino acid sequence that differs in at least one position from the amino acid sequence of the insulin-related peptide. A
30 "physiologically active fragment" of an insulin, insulin analog, insulin-related peptide or insulin-related peptide analog is a molecule that includes less than the full amino acid sequence of the respective peptide but that has substantially the same physiological activity as the complete peptide, preferably at least about 70% of the activity of the complete peptide.

Also as used herein, an "insulin sensitizer" is a compound that increases a patient's response to, or decreases the patient's resistance to, insulin.

5 For present purposes, all references to "insulin", "insulin analog" and "insulin-related peptide" will encompass analogs and physiologically active fragments of such molecules.

A first preferred embodiment of the inventive pharmaceutical composition combines therapeutically effective amounts of an insulin with an
10 insulin-related peptide. More preferably, this embodiment also includes a non-ionic surfactant. Use of non-ionic surfactants according to the invention affords thermally stable compositions. Non-ionic surfactants according to the invention are used to create safe domains which protect the relatively more thermally unstable insulin-related peptides. The protection afforded by
15 the surfactants enables effective co-administration of the insulin and the selected insulin-related peptide.

The inventive compositions according to this embodiment preferably include an insulin selected from the group consisting of human insulin, porcine insulin and bovine insulin. Combinations of two or more different
20 insulins can also be used. The insulin can be a naturally occurring insulin, a semisynthetic insulin, a synthetic insulin or a recombinant insulin.

Insulin analogs that are useful according to the invention include, without limitation, "Lyspro" (commercially available from Eli Lilly Co.), Lys^{B28} insulin, Pro^{B29} insulin and Asp^{B28} insulin. Other insulin analogs that are
25 useful according to the invention are described, e.g., in U.S. Patent No. 5,149,777 and U.S. Patent No. 5,514,646, which are incorporated herein by reference. Combinations of two or more insulin analogs can also be used.

Insulin-related peptides that are useful according to the invention include, without limitation: C-peptide, which is useful in protecting
30 microvasculature against glycosylation-related damage, and which in addition delays gastric emptying; GLP-1, which also delays gastric emptying; amylin; IGF-1, which functions to maintain glucostasis; and IGF-1 bound to binding protein 3 (somatokine), which does not produce hyperglycemia and is therefore particularly useful for treating type 2 diabetes.

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Non-ionic surfactants useful according to this embodiment of the invention include, without limitation, block copolymers of propylene oxide and ethylene oxide. Exemplary surfactants include those commercially available from the BASF Corporation under the name Pluronic®, such as Pluronic F20, Pluronic F28, Pluronic F68, Tween 20, Tween 40 and Brij, and those commercially available under the name Genapol®, such as Genapol 1800. The non-ionic surfactant preferably is pharmaceutically acceptable. Combinations of two or more non-ionic surfactants can also be used.

When a non-ionic surfactant is used, preferably, the amount of the non-ionic surfactant in the composition is less than that which results in a two-phase composition. That is, the concentration of the surfactant in the composition is below the critical micellar concentration of the composition. The critical micellar concentration will vary depending on the particular agents used to form the composition, but is readily determined by those skilled in the art through routine experimentation.

Thus, in the foregoing preferred embodiment, the inventive composition preferably includes about 1.5 to about 40 mg/ml of the insulin or combination of insulins, more particularly about 3.5 to 3.5 mg/ml, about 1.5 to about 40 mg/ml, more particularly about 4 to 10 mg/ml, of the selected insulin-related peptide(s), and an amount of the selected surfactant(s) such that the concentration of the selected surfactant in the composition is less than the critical micellar concentration.

At lower surfactant concentrations, a "micro" two-phase composition is formed in which the surfactant coats the hydrophobic portions of the insulin-related peptide. This surfactant coating also increases the thermal stability of the peptide. Thus, in another preferred embodiment of the invention, a pharmaceutical composition is provided which includes i) an insulin and ii) an insulin-related peptide that includes a hydrophobic portion that is coated with a non-ionic surfactant. The amount of the non-ionic surfactant present in the composition preferably is sufficient to completely coat all hydrophobic portions of the insulin-related peptide.

A more specific preferred embodiment of the foregoing pharmaceutical composition further includes a therapeutically effective amount of at least one insulin sensitizer. Preferred insulin sensitizers include

compounds of the glitazone family. These include, for example, the compounds described in U.S. Patent No. 5,753,681, incorporated herein by reference, such as troglitazone, pioglitazone, englitazone and related
5 compounds. When insulin sensitizers are included in the foregoing pharmaceutical composition, they preferably are present in amounts ranging from 0.2 to 1.4 mg/ml, more preferably about 0.5 to 0.8 mg/ml.

According to a second preferred embodiment, the inventive pharmaceutical composition includes an insulin and an insulin sensitizer (i.e.,
10 agents i) and iii)). The amounts of the insulin and insulin sensitizer are typically the same as those set forth in connection with the preceding embodiment, i.e., about 1.5 to 40 mg/ml, more particularly about 3.5 to 14 mg/ml of an insulin or combination of insulins, and about 0.2 to 1.4 mg/ml, more particularly about 0.5 to 0.8 mg/ml of one or more insulin sensitizers.

15 According to a third preferred embodiment, the inventive pharmaceutical composition includes an insulin-related peptide and an insulin sensitizer (i.e., agents ii) and iii)). The amounts of the insulin and insulin sensitizer are typically the same as those set forth in connection with the preceding embodiment, i.e., about 1.5 to 40 mg/ml, more particularly about
20 4 to 10 mg/ml of an insulin-related peptide or combination of insulin-related peptides, and about 0.2 to 1.4 mg/ml, more particularly about 0.5 to 0.8 mg/ml of one or more insulin sensitizers.

The inventive compositions are preferably formulated to include one or more pharmaceutically acceptable carriers and optionally additional
25 conventional excipients such as diluents, buffers, preservatives, pH adjusters, etc. The compositions can be prepared by a variety of known techniques, for example those described in *Remington's Pharmaceutical Sciences*, 17th Edition, Mack Publishing Company, Easton, PA, USA (1985), which is incorporated herein by reference.

30 The inventive compositions are particularly useful in treating patients suffering from diabetes together with one or more diabetes side effects. The compositions can be administered to patients in need of such treatment by any desired route, such as subcutaneous, pulmonary, etc. In particular, the inventive compositions can be administered by means of medication infusion
35 pumps, which can be reusable or non-reusable (i.e., disposable), and

implantable or externally mountable. Medication infusion pumps that are usefully employed for this purpose include, without limitation, the pumps disclosed in copending, commonly assigned U.S. Patent Applications Serial

5 No. 09/253,382 and 09/253,383, filed February 19, 1999; in U.S. Patent No. 5,637,095, to Nason et al., entitled "Medication Infusion Pump with Flexible Drive Plunger"; in U.S. Patent No. 5,569,186, to Lord et al., entitled "Closed Loop Infusion Pump System with Removable Glucose Sensor"; and

10 Medication Pump with Implantable Pressure Reservoir". The compositions can be administered continually from such devices, or can be administered intermittently.

According to one method of the invention, a pharmaceutical composition that includes two or more of agents i) – iii) as described is

15 administered to a patient in need of such treatment.

According to an alternative method of treatment, two (or more) separate compositions are administered to the patient, either simultaneously or sequentially, and more specifically using separate delivery devices and delivery rates for each composition.

20 Each such composition includes one (or more) of agents i) – iii) as described herein.

The invention is further illustrated by the following non-limiting examples.

5 Example 1

Insulin	4 mg/ml
C-Peptide	2.5 mg/ml
Genapol 1800	17 ug/ml
Glycerin	16 mg/ml
Zinc	0.36 mg/ml
Phosphate buffer	1.96 mg/ml

PH 7.4

10 The composition is suitable for administration using an externally mounted medication infusion pump.

Example 2

Insulin	15.8 mg/ml
GLP-1	4.1 mg/ml
Pluronic F20	0.11 mg/ml
Glycerin	16 mg/ml
Zinc	0.36 mg/ml
Phosphate buffer	1.96 mg/ml

15 PH 7.0-7.8

The composition is suitable for administration using an implantable medication infusion pump.

Example 3

Insulin	4 mg/ml
IGF-1	1.1 mg/ml
Tween 20	0.1 mg/ml
Glycerin	16 mg/ml
Zinc	0.36 mg/ml
Phosphate buffer	1.96 mg/ml

5 Example 4

Insulin	4 mg/ml
IGF-1 bound to binding protein 3	2.2 mg/ml
Tween 40	0.1 mg/ml
Glycerin	16 mg/ml
Zinc	0.36 mg/ml
Phosphate buffer	1.96 mg/ml

Example 5

Lys ^{B28} Pro ^{B29} insulin	4 mg/ml
C-peptide	2.5 mg/ml
Genapol	0.01 mg/ml
Glycerin	16 mg/ml
Zinc	0.36 mg/ml
Phosphate buffer	1.96 mg/ml

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Example 6

Insulin	4 mg/ml
Troglitazone	1.1 mg/ml
Phosphate buffer	1.96 mg/ml

5 Example 7

Insulin	15.8 mg/ml
C-peptide	2.5 mg/ml
Troglitazone	1.0 mg/ml
Genapol	0.01 mg/ml
Glycerin	16 mg/ml
Zinc	0.36 mg/ml
Phosphate buffer	1.96 mg/ml

In alternative embodiment, the insulin and/or insulin analog are replaced by an insulin mimetic material that functions to activate the human insulin receptor. Examples of suitable insulin mimetic materials are shown and described in U.S. Provisional Patent Application Serial No. 60/135,278 filed on May 21, 1999 and entitled "Device and Method for Infusion of Small Molecule Insulin Mimetic Materials, which is specifically incorporated by reference herein and forms a part of this disclosure.

While the description above refers to particular embodiments of the present invention, it will be understood that many modifications may be made without departing from the spirit thereof. The accompanying claims are intended to cover such modifications as would fall within the true scope and spirit of the present invention.

The presently disclosed embodiments are therefore to be considered in all respects as illustrative and not restrictive, the scope of the invention being indicated by the appended claims, rather than the foregoing description, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

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WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising at least two of agents i) –
 5 iii), wherein
 agent i) is selected from the group consisting of an insulin, an insulin analog, a physiologically active fragment of said insulin and a physiologically active fragment of said insulin analog,
 agent ii) is selected from the group consisting of an insulin-related
 10 peptide, an insulin-related peptide analog, a physiologically active insulin-related peptide fragment and a physiologically active insulin-related peptide analog fragment, and
 agent iii) is an insulin sensitizer.
- 15 2. The composition of claim 1 wherein said agent i) is an insulin.
3. The composition of claim 2 wherein said insulin is selected from the group consisting of human insulin, porcine insulin and bovine insulin.
- 20 4. The composition of claim 1 wherein said agent i) is an insulin analog.
5. The composition of claim 4 wherein said insulin analog is selected from the group consisting of Lys^{B28} insulin, Pro^{B29} insulin and Asp^{B28} insulin.
- 25 6. The composition of claim 1 wherein said agent ii) is an insulin-related peptide.
7. The composition of claim 6 wherein said peptide is selected from the group consisting of C-peptide, GLP-1, amylin, IGF-1 and IGF-1 bound to
 30 binding protein 3.
8. The composition of claim 1 wherein said agent iii) is an insulin sensitizer of the glitazone family.

9. The composition of claim 1 which is stabilized for administration by a medication infusion pump.
- 5 10. The composition of claim 1 comprising agent i) and agent ii).
11. The composition of claim 1 comprising about 1.5 to about 40 mg/ml of agent i) and about 1.5 to about 40 mg/ml of agent ii).
- 10 12. The composition of claim 10 further comprising a pharmaceutically acceptable non-ionic surfactant.
13. The composition of claim 12 wherein said non-ionic surfactant is a block copolymer of propylene oxide and ethylene oxide.
- 15 14. The composition of claim 13 comprising about 1.5 to about 40 mg/ml of agent i), about 1.5 to about 40 mg/ml of agent ii) and an amount of said non-ionic surfactant affording a concentration less than the critical micellar concentration of said composition.
- 20 15. The composition of claim 9 further comprising agent iii).
16. The composition of claim 1 comprising agent i) and agent iii).
- 25 17. The composition of claim 16 comprising about 0.5 to about 40 mg/ml of agent i) and about 0.05 to about 12 mg/ml of agent iii).
18. The composition of claim 1 comprising agent ii) and agent iii).
- 30 19. The composition of claim 18 comprising comprising about 0.05 to about 12.5 mg/ml of agent ii) and about 0.05 to about 12.5 mg/ml of agent iii).
20. The composition of claim 1 comprising two or more compounds of
35 agents i), ii) or iii).

21. A pharmaceutical composition comprising
- 5 i) at least one agent selected from the group consisting of an insulin, an insulin analog, a physiologically active insulin fragment and a physiologically active insulin analog fragment and
- ii) at least one agent selected from the group consisting of an insulin-related peptide, an insulin-related peptide analog, a physiologically active insulin-related peptide fragment and a physiologically active insulated-related peptide analog fragment,
- 10 wherein said agent ii) comprises a hydrophobic portion that is coated with a pharmaceutically acceptable non-ionic surfactant.
22. The pharmaceutical composition of claim 21 wherein said non-ionic surfactant is a block copolymer of propylene oxide and ethylene oxide.
- 15 23. The pharmaceutical composition of claim 21 further comprising a pharmaceutically acceptable carrier.
24. The pharmaceutical composition of claim 21 further comprising iii) an
- 20 insulin sensitizer.
25. The composition of claim 21 which is stabilized for administration by a medication infusion pump.
- 25 26. A method of treating diabetes comprising the step of administering to a patient in need of such treatment the pharmaceutical composition of claim 1.
27. The method of claim 26 wherein said composition is administered to
- 30 said patient by a medication infusion pump.
28. The method of claim 27 wherein said medication infusion pump is reusable.

29. The method of claim 27 wherein said medication infusion pump is non-reusable.
- 5 30. The method of claim 27 wherein said medication infusion pump is implantable.
31. The method of claim 27 wherein said medication infusion pump is externally mountable.
- 10 32. The method of claim 26 wherein said composition is administered continually.
- 15 33. A method of treating diabetes comprising the step of administering to a patient in need of such treatment the pharmaceutical composition of claim 10.
- 20 34. A method of treating diabetes comprising the step of administering to a patient in need of such treatment the pharmaceutical composition of claim 12.
- 25 35. A method of treating diabetes comprising the step of administering to a patient in need of such treatment the pharmaceutical composition of claim 15.
- 30 36. A method of treating diabetes comprising the step of administering to a patient in need of such treatment the pharmaceutical composition of claim 16.
37. A method of treating diabetes comprising the step of administering to a patient in need of such treatment the pharmaceutical composition of claim 18.
- 35 38. The method of claim 37 wherein said diabetes is type 2 diabetes.

39. A method of treating diabetes comprising the step of administering to a patient in need of such treatment the pharmaceutical composition of claim 20.

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40. A method of treating diabetes comprising the step of administering to a patient in need of such treatment the pharmaceutical composition of claim 21.

10 41. A method of treating diabetes comprising the step of administering to a patient in need of such treatment at least two pharmaceutical compositions a)-c), wherein

composition a) comprises

- 15 i) at least one agent selected from the group consisting of an insulin, an insulin analog, a physiologically active fragment of said insulin and a physiologically active fragment of said insulin analog, and
- ii) a pharmaceutically acceptable carrier,

composition b) comprises

- 20 i) at least one agent selected from the group consisting of an insulin-related peptide, an insulin-related peptide analog, a physiologically active insulin-related peptide fragment and a physiologically active insulin-related peptide analog fragment, and
- ii) a pharmaceutically acceptable carrier, and

25 composition c) comprises

- i) an insulin sensitizer, and
- ii) a pharmaceutically acceptable carrier.

42. The method of claim 41 wherein each of said compositions is
30 administered to said patient using a separate delivery device.

43. The method of claim 42 wherein each said delivery device is a medication infusion pump.

- 44 The method of claim 41 wherein each of said compositions is administered at a different rate.
- 5 45. The method of claim 41 wherein each of said compositions is administered continually.
46. The method of claim 41 wherein compositions a) and b) are administered to said patient.
- 10 47. The method of claim 46 wherein said composition b) further comprises at least one pharmaceutically acceptable non-ionic surfactant.
48. The method of claim 41 wherein compositions a) and c) are administered to said patient
- 15 49. The method of claim 41 wherein compositions b) and c) are administered to said patient
- 20 50. The method of claim 41 wherein compositions a), b) and c) are administered to said patient.
51. A method of making a pharmaceutical composition useful in treating diabetes, said method comprising the step of combining at least two of agents i) – iii), wherein
- 25 agent i) is selected from the group consisting of an insulin, an insulin analog, a physiologically active fragment of said insulin and a physiologically active fragment of said insulin analog,
- agent ii) is selected from the group consisting of an insulin-related peptide, an insulin-related peptide analog, a physiologically active insulin-related peptide fragment and a physiologically active insulin-related peptide analog fragment, and
- 30 agent iii) is an insulin sensitizer.

52. The method of claim 51 wherein said agents are combined with a pharmaceutically acceptable carrier.
- 5 53. The method of claim 51 wherein agents i) and ii) are combined.
54. The method of claim 52 wherein agents i) and ii) are combined with a pharmaceutically acceptable non-ionic surfactant.
- 10 55. The method of claim 51 wherein agents i) and iii) are combined.
56. The method of claim 51 wherein agents ii) and iii) are combined.
57. The method of claim 51 wherein agents i), ii) and iii) are combined.
- 15 58. A method of treating diabetes and at least one side effect thereof which comprises the step of administering to a patient in need of such treatment a pharmaceutical composition comprising
- a) at least one agent selected from the group consisting of an
- 20 insulin, an insulin analog, a physiologically active insulin fragment and a physiologically active insulin analog fragment,
- b) at least one agent selected from the group consisting of an insulin-related peptide, an insulin-related peptide analog, a physiologically active insulin-related peptide fragment and a physiologically active insulin-
- 25 related peptide analog fragment, wherein said agent is effective in treating said side effect, and
- c) a pharmaceutically acceptable non-ionic surfactant.

59. A pharmaceutical composition comprising at least two of agents i) –
iii), wherein
agent i) is selected from the group consisting of an insulin mimetic
5 material,
agent ii) is selected from the group consisting of an insulin-related
peptide, an insulin-related peptide analog, a physiologically active insulin-
related peptide fragment and a physiologically active insulin-related peptide
analog fragment, and
10 agent iii) is an insulin sensitizer.
60. The composition of claim 59 wherein said agent i) is a small molecule
insulin.
- 15 61. The composition of claim 60 wherein the small molecule insulin
mimetic material is L-783,281.
62. The composition of claim 59 wherein said agent ii) is an insulin-
related peptide.
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63. The composition of claim 62 wherein said peptide is selected from
the group consisting of C-peptide, GLP-1, amylin, IGF-1 and IGF-1 bound to
binding protein 3.
- 25 64. The composition of claim 59 wherein said agent iii) is an insulin
sensitizer of the glitazone family.
65. The composition of claim 59 which is stabilized for administration by
a medication infusion pump.
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66. The composition of claim 59 comprising agent i) and agent ii).
67. The composition of claim 66 further comprising a pharmaceutically
acceptable non-ionic surfactant.
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68. The composition of claim 67 wherein said non-ionic surfactant is a block copolymer of propylene oxide and ethylene oxide.
- 5 69. The composition of claim 65 further comprising agent iii).
70. The composition of claim 59 comprising agent i) and agent iii).
71. The composition of claim 59 comprising two or more compounds of
10 agents i), ii) or iii).